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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,410	06/23/2006	James Peter Burnie	22083-007US1 / WA/MP10039	2177

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
09/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,410	BURNIE ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14,17-23,26,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,13,14,17-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

2. The drawings in this application have been accepted. No further action by Applicant is required.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

4. The information disclosure statement filed on 9/23/2005 has been considered. An initialed copy is enclosed.

Election/Restrictions

5. Applicant's election with traverse of Group III claims 10-11, 13-15, and 21-25 are acknowledged. The traversal is on the ground(s) that the election is made with traverse. To provide a clear record, applicants wish to state their position on Cerquetti (Cerquetti et al., Microbial Pathogenesis, 13:271-279, 1992). According to the Office Action, Cerquetti discloses a Clostridium difficile lactate dehydrogenase. More specifically, the Office Action states: The technical feature of Group I Clostridium difficile lactate dehydrogenase. The technical feature of Group 1 is anticipated by Cerquetti et al [reference omitted]. Cerquetti et al teach a 36 kDa immunodominant antigen of Clostridium difficile as determined by SDS and elicits precipitating antibodies in rabbits .... and recognizes antibodies present within sera. Therefore the Clostridium difficile lactate dehydrogenase of Cerquetti et al anticipates the Clostridium difficile lactate

dehydrogenase of the present application (see page 2 of the Office Action). Applicants respectfully submit that Cerquetti merely discloses a molecule that they refer to as "the 36 kDa antigen" (272, paragraph 2). Cerquetti fails to provide any evidence, explicit or implicit, that the 36 kDa antigen is lactate dehydrogenase. Nevertheless, the Office appears to have assumed that the 36 kDa antigen disclosed by Cerquetti is lactate dehydrogenase.

Applicants submit that the Office has provided no evidence to support this assumption. Without further evidence, the 36 kDa antigen could be any 36 kDa molecule derived from C. difficile, and not necessarily C. difficile lactate dehydrogenase. Applicants respectfully submit, therefore, that Cerquetti does not anticipate the technical feature of Group I. Thus, Cerquetti does not appear to destroy the unity of the claims, and applicants respectfully request examination of all the pending claims as a single group.

Examiner accepts Applicant's arguments. Therefore the restriction is withdrawn and all claims (1-11, 13-14, 17-23, 26, and 28-29) are considered.

There are no claims that withdrawn from further consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 10-11, 13-14, 17-23, 26 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980).

Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegratin.g Co., 90 US 566 (1974);American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). In the instant case recitation of an antibody does not indicate the hand of man because an antibody are naturally occurring, therefore the claimed antibody composition is deemed a product of nature. Applicant(s) can recite, for example "isolated antibody" provided there is support in the disclosure to reflect the hand of man for the product and method using the product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 14, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabled for any method of treating Clostridium difficile infection in a patient/subject, comprising administering to the patient a pharmaceutically effective amount of the antibody or fragment thereof of claim 10; or comprising administering a pharmaceutically effective amount of the composition of claim 13.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims. The claim is very broad. The claims are drawn to product using the method of treating Clostridium difficile infection in a patient/subject. The quantity of experimentation required to practice the invention as claimed would require in vivo and in vitro studies of the antibody or fragment thereof that is binding to an amino acid of SEQ ID NO: 2. Since the specification fails to provide particular guidance for the treating Clostridium difficile infection in a patient/subject, comprising administering to the patient a pharmaceutically effective amount of the antibody or fragment threreof of claim 10; or comprising administering a pharmaceutically effective amount of the composition of claim 13, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Nature of the invention. The claims are drawn to a method of treating any Clostridium difficile infection in a patient/subject, comprising administering to the patient a pharmaceutically effective amount of the antibody or fragment threreof of claim 10; or comprising administering a pharmaceutically effective amount of the composition of

claim 13. The specification discloses, immunoblotting experiments using fractionated C. difficile protein extracts and antisera obtained from patients infected with C. difficile that protein of apparent molecular weight 36 Kda (see pg. 13). The specification discloses the antibody responses against immunodominant antigens of C. difficile (see pg. 23).

Guidance of the specification: The specification suggest that antibody that binds to SEQ ID NO: 2 can be use to treat Clostridium difficile (see pgs. 13-27). The specification does not show a successful uptake of an effector at the target site in a sufficient amount to generate a therapeutic effect in vivo for any treatment of Clostridium difficile. The specification does not disclose any in vitro or in vivo working examples (i.e. challenged mice models or passive immunization approaches) that the method of administering to any subject a therapeutically effective amount of the antibody, antigen fragment, or fragment thereof that binds to SEQ ID NO: 2 will work or be effective in any treatment of Clostridium difficile. There is not empirical data reported in the specification at the time of filing showing efficacy of the antibody, antigen fragment, or fragment thereof of binding SEQ ID NO: 2. Therefore, the specification as filed fails to provide particular guidance demonstrating a reasonable extrapolation which resolves the known unpredictability in the art in any subject provided in vivo in any and/or all organisms whereby treatment effects are provided in any and/or all organisms. The skilled artisan would clearly realize the critical deficiency of this specification with respect to Clostridium difficile.

The state of the prior art. The state of the art indicate teach compositions including a soy product and an active immunoglobulin for nutrition and overall health benefits to humans and animals. The art indicate that active immunoglobulins can be collected from a human or animal that has been specifically immunized against antigenic targets *Clostridium difficile*, toxins (*C. difficile* toxins A and B (see pg. 12). The art indicate method of treating *Clostridium difficile* infection comprising administering to a patient in need thereof an effective dose of a pharmaceutical composition comprising: polyclonal antibodies directed against at least one enteric pathogen; and a probiotic,

wherein the probiotic is *Bifidobacterium*, or *Lactobacillus*, wherein the pharmaceutical composition is microencapsulated, wherein the polyclonal antibodies are raised against more than one antigen derived from *Clostridium difficile*, wherein the pharmaceutical composition is in combination with a suitable food product, wherein the food product is a yogurt or a yogurt-based drink, wherein the antigen is *Clostridium difficile* Toxin A and *Clostridium difficile* Toxin B (see Bostwick et al WO 00/24266 in its entirety). The art indicate, a method of treating *Clostridium difficile* infection comprising administering to a patient in need thereof an effective dose of a pharmaceutical composition comprising: polyclonal antibodies directed against at least one enteric pathogen (see pages abstract, 5-8 Chandler et al WO 97/20577). The art indicates active and passive immunization methods for preventing and treating *Clostridium difficile* infection, which involve administration of C. difficile toxin-neutralizing polyclonal immune globulin with a patient that has or is at risk of developing recurrent *Clostridium difficile* associated diarrhea (see US Patent 6,969,520 Thomas et al in its enitirety). The art indicates the parenteral *C. difficile* toxoid vaccine clearly induces vigorous serum anti-toxin A antibody responses in healthy adults. However, whether these vaccine-induced immune responses can confer protective immunity against *C. difficile*-associated diarrhea and colitis remains to be proven. The art indicates that clinical trials were initiated to determine whether the *C. difficile* toxoid vaccine induces similarly rapid and robust anti-toxin A antibody responses in elderly individuals and in patients with recurrent *C. difficile*-associated diarrhea who, as they have shown, fail to mount an appropriate, protective immune response to toxin A during natural challenge with *C. difficile* (see pg. 1610 last paragraph Aboudola et al Infection and Immunity 2003 pgs. 1608-1610).

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further

teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally as evidenced by Greenspan et al. (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, Or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the state of the art remains unpredictable.

Working examples. The specification does not give any working example (i.e. challenged mice models or passive immunization approaches).

In conclusion, the claimed inventions are not enabled for a method of treating any Clostridium difficile infection in a patient/subject, comprising administering to the patient a pharmaceutically effective amount of the antibody or fragment thereof of claim 10; or comprising administering a pharmaceutically effective amount of the composition of claim 13. There is a lack of working examples. The specification does not show a successful uptake of an effector at the target site in a sufficient amount to generate a therapeutic effect in vivo for any treatment of Clostridium difficile. The specification does not disclose any in vitro or in vivo working examples (i.e. challenged mice models or

passive immunization approaches) that the method of administering to any subject a therapeutically effective amount of the antibody or antigen fragment that binds to SEQ ID NO: 2 will work or be effective in any treatment of Clostridium difficle. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Status of the Claims

8. No claims are allowed.

Claims 10-11, 13-14, 17-23, 26 are rejected.

Claim 25 is objected as being dependent on a cancelled claim.

Claims 1-9 and 28-29 are free of the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisors, Shanon Foley can be reached on 571-272-0898 and Robert Mondesi at 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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